Nitrile-forming Eliminations from Oxime Ethers

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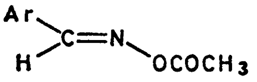
The oxime ethers (7) and (8) (R = alkyl or aryl) undergo base-catalysed elimination to benzonitriles (3) in water–dioxan (4 : 1) at 25°. The *Z*-isomer (8*Z*) reacts *via* hydroxide-catalysed antiperiplanar elimination 70-fold more rapidly than the corresponding *E*-isomer. Electronic effects on *syn*-elimination (from 7*E*) show that electron-withdrawing groups aid elimination in both Ar and in the leaving group $^-$OR; no intramolecular assistance is observed in these substrates. These results are interpreted in terms of a central *E*2 elimination, with appreciable C–H and N–O$^-$ bond cleavage in the transition state.

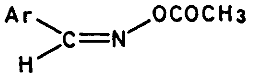
THE dehydration of aldoximes (2) is a reaction which permits the transformation of an aldehyde (1) to the corresponding nitrile (3) under mild conditions and in high overall yield.[1,2] Aldoximes (2) themselves can rarely be dehydrated in the presence of basic reagents, being usually converted into their corresponding anions.[3] Exceptions to this are the observed eliminations in dilute alkaline solution when the methine hydrogen in (2) is activated, *e.g.* Ar = *o*-$NO_2C_6H_4$.[3,4]

$$\underset{(1)}{ArCHO} + NH_2OH \longrightarrow \underset{(2)}{ArCH{=}NOH} \xrightarrow{-H_2O} \underset{(3)}{ArC{\equiv}N}$$

The most widely used reagent for effecting the dehydration (2) ⟶ (3) is acetic anhydride.[5,6] *O*-Acetylbenzaldoximes (4) or (5) have been shown to be intermediates in this reaction and although the relative reactivities of the *E*- and *Z*-isomers was at one time controversial,[7-9] it is now clear [10-12] that the *Z*-isomer (5*Z*) gives predominantly nitrile when reacted with base above 30° while hydrolysis to give the oxime predominates at all temperatures for the *E*-isomer (4*E*) and at 0° for (5*Z*).



(4*E*)



(5*Z*)

$$ArCH{=}NOR$$

(6)

Electron-withdrawing substituents in Ar increase the proportion of nitrile formation from (5*Z*). Two factors may contribute to the relative lack of elimination from (4*E*) in base, (a) the proximity of the $OCOCH_3$ group may hinder the approach of the base to the methine hydrogen and (b) elimination must occur with *syn*-stereospecificity which may be energetically less favourable.[12,13] Pyrolytic elimination, on the other hand, occurs most readily from the isomer (4*E*), and a concerted mechanism involving simultaneous C–H and N–O bond cleavage has been proposed.[14]

In addition to acetic anhydride a wide variety of other reagents have more recently been used to dehydrate aldoximes (2) to nitriles (3). These include acetyl chloride,[15] thionyl chloride,[16] ethyl chloroformate,[17] 2,4-dinitrochlorobenzene,[18] phosphorus pentaoxide,[19] benzoyl chloride,[20] α,β-dibromopropiononitrile,[21] triethyl phosphate,[22] phenyl isocyanate,[23] arenesulphonyl chlorides,[24,25] methanesulphonyl chloride,[26] dialkyl hydrogenphosphonates and CCl_4,[27] 3-chloro-1,2-benzisothiazole *SS*-dioxide,[28] *p*-chlorophenyl chlorothionoformate,[29] phenyl chloroformate,[30] triphenylphosphine and CCl_4,[31] titanium tetrachloride,[32] cyanuric chloride,[33] 1,1′-dicarboxybi-imidazole,[34] trichloroacetonitrile,[35] phosphonitrilic chloride,[36] carbodi-imides in the presence of Cu^{II},[37] triethyl orthoesters,[38] *NN*-dimethyldichloromethyleneaminium chloride,[39] phenyl chlorosulphite,[40] triflic anhydride,[41] toluene-*p*-sulphonic acid,[42] and 1-(*NN*-diethylamino)propyne.[43] The *E*- (or *syn*-) aldoxime was normally used (if configuration was specified) but the *Z*-aldoxime was used in some cases.[29,30,34,36] Intermediates of type (6) were suggested as the primary products in many cases but only rarely isolated.[30,36,38]

No detailed studies have, however, been carried out on the general mechanism of these nitrile-forming eliminations when the *cis*-pyrolysis pathway is blocked. We now report on a study of base-catalysed eliminations from *O*-alkyl- and *O*-aryl-aldoximes (6; R = alkyl or aryl) to the corresponding nitriles. A range of *E*-oxime ethers were prepared and their reactivity examined as a function of Ar and R. In addition a single *Z*-oxime ether (8; Ar = *p*-$NO_2C_6H_4$, R = Me) was examined in order to determine if the preference for *anti*-elimination observed in alkene- and in alkyne-forming eliminations [44] was also evident in nitrile formation.

RESULTS AND DISCUSSION

Preparation of Oxime Ethers and Configurational Assignments.—The *E*-oxime ethers (7a—i) were prepared by various techniques. Literature syntheses of compounds (7a),[45] (7i),[46] and (8a) [45] are available. Attempts to obtain *Z*-*O*-arylaldoximes (8; R = aryl) were unsuccessful. For example, the silver salt of *Z*-*p*-nitrobenzaldoximate failed to react with 2,4-dinitrochlorobenzene even under forcing conditions (possibly due to steric hindrance in the product). Direct condensation to aldehydes with substituted phenoxyamines led to a single isomer shown to be the (presumably more

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stable) *E*-ether (7; R = aryl). This latter procedure was used to form ethers (7a—d) and (7f—h).

The methyl ethers formed on methylation of the benzaldoxime isomers (whose configuration is known) [47] were assumed to have retained the configuration of the oxime. This is not unreasonable in view of the slow rate of isomerisation of oximes under basic conditions.[48] The oxime formed from ω-isonitrosoacetophenone (2; Ar = PhCO) is believed to be the *E*-isomer.[49] This assignment is also consistent with ^{1}H n.m.r. evidence; the methine resonance is at δ 8.10 in DMSO, which is within the range of other *E*- (but not *Z*-) aldoximes.[47]

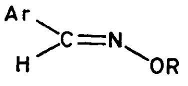
TABLE 1

Second-order rate constants for the hydroxide ion catalysed conversion of oxime ethers to nitriles [a]

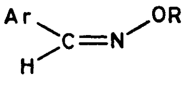
Oxime ether	$10^5k_{HO^-}$/l mol^{-1} s^{-1}	λ/nm [b]	pH [c]
(7a)	1.84	320	14.0
(7b)	61 700	310	12.5—13.0
(7c)	1 740	320	13.0—14.0
(7d)	63	350	13.0—14.0
(7e)	3 980	310	12.5—14.0
(7f)	42.2	305	13.0—14.0
(7g)	1.52	268	14.0
(7h)	20 000	320	13.0—14.0
(7i)	112 000	290	10.25—13.0
(8a)	135	310	13.0—14.0

[a] At 25°; μ = 1.0 (NaCl), 7 : 3 v/v water–dioxan. [b] Wavelength at which reaction was studied. [c] pH (or pH range) at which reaction was studied.

In several cases the *E*-oxime ethers (7; R = aryl) were prepared by the two independent routes, *viz.* arylation of the oximate anion and reaction of the aldehyde with an aryloxyamine. Identical products were obtained in both cases, indicating that the latter route leads to *E*-ethers in each case. This is also consistent with literature data [50] for the formation of (7h); moreover the kinetic results reported below also support these assignments.



(7*E*)

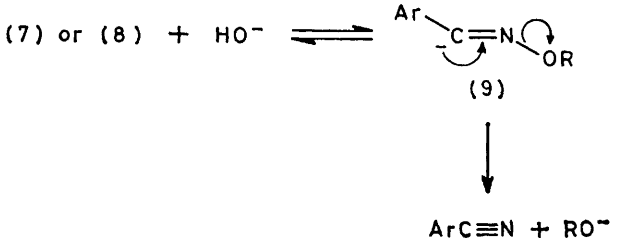


(8*Z*)

a; Ar = p-$NO_2C_6H_4$, R = Me
b; Ar = p-$NO_2C_6H_4$, R = 2,4-$(NO_2)_2C_6H_3$
c; Ar = p-$NO_2C_6H_4$, R = p-$NO_2C_6H_4$
d; Ar = p-$NO_2C_6H_4$, R = Ph
e; Ar = Ph, R = 2,4-$(NO_2)_2C_6H_3$
f; Ar = Ph, R = p-$NO_2C_6H_4$
g; Ar = Ph, R = Ph
h; Ar = o-$NO_2C_6H_4$, R = p-$NO_2C_6H_4$
i; Ar = Bz, R = Me

Kinetic Results.—The rates of reaction of the oxime ethers (7) and (8) to the corresponding nitriles (3) were followed in 7 : 3 water–dioxan at 25° using u.v. spectroscopy. (Dioxan–water was used since the ethers were insoluble, even at the low concentrations used, in pure water.) The results are summarised in Table 1; in each case a simple first-order dependence of [HO$^-$] was observed (plots not shown) and the derived second-order rate constants in Table 1 are average values determined at several pH values (the range studied is also listed in this Table).

The products formed were the corresponding nitriles as confirmed by (a) actual isolation when the experiments were carried out on a large scale, (b) the identity of the u.v. spectrum of an authentic mixture of RO$^-$ and ArC≡N with the product formed from the corresponding oxime ether, and (c) the presence of a slow subsequent reaction for oxime ethers (7a—d) at pH 14; this slow reaction corresponded to the rate of hydrolysis of authentic *p*-nitrobenzonitrile.



SCHEME

There was no evidence, even with those ethers carrying the most highly electron-withdrawing substituents [*e.g.* (7b)] for the rate of elimination becoming pH independent at high pH. Such behaviour might be expected if reaction were occurring *via* the conjugate base (9) (Scheme). In order to test this possibility further we have also examined the aroyl-substituted ether (7i); the benzoyl group is expected particularly to stabilize the conjugate base (9; Ar = Bz). Although this ether underwent very rapid elimination, the rate of elimination was strictly proportional to [HO$^-$], even at [HO$^-$] 0.1M. Clearly therefore the pK_a of (7i) ⩾ 14. We have also checked the possibility that the reaction being followed in this case was not the elimination from the oxime ether (7i) but hydrolysis of the nitrile (3; Ar = Bz) formed, by investigating independently the rate of hydrolysis of the latter. The observed rate constants are listed in Table 2 and are correlated by equation (1) with k_{H_2O} 8.5 × 10^{-3} s^{-1} and k_{HO^-} 4.47 × 10^5 l mol s^{-1}. Similar results have been observed for the hydrolysis of the nitrile (3; Ar = Bz) in water [51] and in 1 : 1 dioxan–water.[52] In any

$$k_{obs.} = k_{HO^-} + k_{H_2O}[HO^-] \qquad (1)$$

event it is clear that this is a very reactive nitrile indeed and that the reaction being measured (Table 1) using (7i) as substrate is the elimination [*i.e.* the formation of (3; Ar = Bz)], even though this was the most reactive oxime ether studied.

TABLE 2

Observed rate constants (s^{-1}) for the hydrolysis of phenylglyoxynitrile (3; Ar = Bz) [a]

pH	4.03	5.44	6.55	7.02	7.51
$10^3k_{obs.}$	8.50	11.4	24.4	61.5	148

[a] Followed at 296 nm; solvent water–dioxan (4 : 1); 25°.

Effect of Oxime Configuration.—By comparing the rates of elimination from the corresponding *Z*- and *E*-isomers (8a) and (7a), it is seen that the *Z*-isomer undergoes base catalysed elimination 73-fold faster than the *E*-isomer. If the reasonable assumption that the H, C, N, and O atoms are in the same plane in both (7) and (8) (R = Me) (as shown by *X*-ray studies on both isomers of *p*-chlorobenzaldoxime),[53] then clearly antiperiplanar elimination is preferred over synperiplanar elimination.

It is to be expected that syn- or anti-periplanar elimination (dihedral angles of 0 and 180°, respectively, between the N-O and C-H bonds) would be favoured over other arrangements but it is not immediately obvious which of these would give the most rapid reaction. Since the C-H and N-O σ bonds become *p*-orbitals in the course of reaction, maximum overlap is achieved when these are mutually parallel. However the preferred antiperiplanar elimination may be attributed to the assistance provided by the displacement of the leaving group (by analogy with the S_N2 reaction) by the bonding electrons in the C-H bond. The preference for antiperiplanar elimination is also generally evidenced in alkene-forming eliminations, although conformational effects which are generally present in these reactions are absent in (7) and (8).

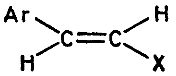
Substituent Effects for E-*Isomers*.—Electron withdrawal in both R and Ar enhances the rate of elimination from (7). Although only a limited number of substituents were used, approximate Hammett ρ values of 1.53, 2.07, and 2.07 can be estimated for the three series with R = 2,4-dinitrophenyl, *p*-nitrophenyl, and phenyl, respectively (Ar varies). These indicate a considerable build-up of negative charge on the carbon of the forming nitrile in the transition state. There is a further 10^5-fold increase in the rate of elimination when the Ar group in (7) changed from *p*-$NO_2C_6H_4$ to Bz, which is in line with this.

The sensitivity to leaving-group variation is also high. This can be expressed in terms of the usual Hammett ρ values or as a Brönsted β for the leaving group ($\beta_{l.g.}$; this is the slope of a plot of log k_{HO^-} against the pK_a of the conjugate acid of the leaving group) which allows the inclusion of both aryloxy and alkoxide leaving groups. For the series (7) with Ar = Ph, $\rho = 2.2$ and $\beta_{l.g.} = -0.58$ while for the series (7), with Ar = *p*-$NO_2C_6H_4$, $\rho = 1.92$ and $\beta_{l.g.} = -0.51$.

Taken together, the substituent effects indicate a concerted mechanism with considerable C-H and N-O bond fission in the transition state. The change in ρ (or $\beta_{l.g.}$) values is also consistent with the Hammond postulate, a ' later ' transition state being expected when Ar = Ph than when Ar = *p*-$NO_2C_6H_4$. A similar conclusion can be reached using a three-dimensional reaction co-ordinate diagram described by More O'Ferrall [54] and Jencks.[55] Thus the carbanionic character of the transition state is increased on changing the leaving group in (7) from R = 2,4-$(NO_2)_2C_6H_3$ to R = *p*-NO_2-C_6H_4. One would therefore expect a shift in the transition state towards the *E*1cB end of the spectrum and this is reflected in leaving-group sensitivities.

The dehydrochlorination of a series of chloro-oximes (10) catalysed by HO^--EtO^- has been studied at 0° in 92.5% ethanol.[56] Although the configuration of these chloro-oximes was not determined, a Hammett ρ value of 2.24 was obtained for substituents in Ar in line with our results. General base catalysis (by amines) of the elimination of HCl from (10) was also observed (Brönsted $\beta = 0.54$) indicating an *E*2 central type of mechanism.[57]

(10)



(11)

syn-Elimination has also been noted in acetylene formation from *trans*-*p*-nitrophenyl-β-halogenoethylenes (11; Ar = *p*-$NO_2C_6H_4$, X = Cl or Br) but only under forcing conditions.[58] Using literature data [58-62] for these eliminations catalysed by Bu^tO^- in Bu^tOH and the rate decrease expected on the transfer from this solvent to HO^--H_2O, it can be estimated that (7b) reacts $>10^6$-fold faster than (11; X = Cl, Ar = *p*-$NO_2C_6H_4$). The nitrile-forming eliminations are therefore appreciably more facile than acetylene formation; this can be ascribed to (a) the fact that an N-heteroatom is undergoing fission in (7) (which is weak because both atoms involved are electronegative) relative to a C-heteroatom in (11) and (b) the greater stability of the nitrile product (the C≡C bond is *ca*. 225 kJ mol^{-1} stronger than C=C, while C≡N is *ca*. 300 kJ mol^{-1} stronger than the corresponding C=N).[63] Since triple-bond formation is well advanced in the transition state (as shown above) such differences in product stability will be reflected in the rates of reaction.

The ortho-*Effect*.—It has been observed that *o*-nitrobenzaldoximes undergo dehydration under conditions where the *p*-isomers do not.[3,4] In order to investigate whether a special mechanism was operative for *o*-substituted ethers we have examined the reactivity of *E*-*O*-(*p*-nitrophenyl)-*o*-nitrobenzaldoxime (7h). As for the *p*-nitro-isomer (7c), elimination to give *o*-nitrobenzonitrile is base-catalysed; no pH-independent rate was observed at 25°. However the observed rate constants (see Table 1) are 11.5-fold faster for the *ortho*-isomer. Similar enhanced reactivity has previously been noted for chloro-oximes (10), but to a less marked extent.[56] Steric facilitation of elimination (leading to the less hindered nitrile) is a possible explanation for these observations; Hauser [56] has noted that an *o*-methyl-substituted chloro-oxime also reacts faster than the *para*-analogue, which would indicate that an electronic effect (*e.g*. a field effect or stronger inductive effect in the *ortho*-position) is unlikely. In any event, the absence of a pH-independent rate rules out intramolecular deprotonation of the aldoxime ether by the *o*-NO_2 group.

EXPERIMENTAL

Substrates.—*E*-(or α-)Benzaldoxime was prepared using the procedure described by Vogel,[64] except that the solution was neutralised (by a rapid stream of CO_2) immediately on addition of the reagents (otherwise, in our hands, considerable quantities of benzyl alcohol resulted). The oxime had m.p. 32—34° (lit.,[65] 34°). The following materials were prepared by literature methods: *E-p*-nitrobenzaldoxime, m.p. (from benzene) 128.5—129° (lit.,[66,67] 128.5—129 and 133°); *Z-p*-nitrobenzaldoxime, m.p. (from ethanol), 107—109° (lit.,[68] 111—112°); *E-O*-methyl-*p*-nitrobenzaldoxime, m.p. 102—104 (lit.,[45,69] 101, 101—102, 105°); *Z-O*-methyl-*p*-nitrobenzaldoxime, m.p. [from light petroleum (b.p. 60—80°)] 60—64° (lit.,[45,69] 67—68°) (Found: C, 53.15; H, 4.5; N, 15.4. Calc. for $C_8H_8N_2O_3$: C, 53.3; H, 4.4; N, 15.6%); *E-O*-2,4-dinitrophenylbenzaldoxime,[70] m.p. (from ethanol) 138—140° (lit.,[50,70,71] 139—140, 143—145°).

A general method was used for the preparation of several of the oxime ethers: the aryloxyamine [*O*-(2,4-dinitrophenyl)hydroxylamine,[72] *O*-(*p*-nitrophenyl)hydroxylamine,[73] or *O*-phenylhydroxylamine [74]] (0.02 mol) was dissolved in ethanol (30 ml) and the aldehyde (0.02 mol) in ethanol (10 ml) added. Hydrochloric acid (0.1 ml) was added and the solution briefly refluxed. On cooling, the oxime ether was precipitated and was recrystallised to constant m.p. from acetic acid. The following materials were prepared by this route: E-O-p-*nitrophenyl*-p-*nitrobenzaldoxime* (7c), a *solid*, m.p. 161—164° (Found: C, 53.7; H, 3.3; N, 14.1. $C_{13}H_9N_3O_5$ requires C, 54.4; H, 3.2; N, 14.6%), δ ([$^2H_6$]DMSO) 7.5—8.6 (two q superimposed on each other, 8 H) and 9.12 (s, 1 H); E-O-*phenyl*-p-*nitrobenzaldoxime* (7d), a yellow *solid*, m.p. 84—87° (Found: C, 62.0; H, 4.0; N, 11.1. $C_{13}H_{10}N_2O_3$ requires C, 64.5; H, 4.1; N, 11.6%), δ (CCl_4) 7.07—7.68 (m, 5 H), 7.8—8.4 (q, 4 H), and 8.5 (s, 1 H); E-O-p-*nitrophenylbenzaldoxime* (7f), a white *solid*, m.p. 118—120° (Found: C, 63.7; H, 4.4; N, 11.3. $C_{13}H_{10}N_2O_3$ requires C, 64.5; H, 4.1; N, 11.6%), δ ([$^2H_6$]DMSO) 7.5—8.5 (q superimposed on m, 9 H) and 8.97 (s, 1 H); E-O-*phenylbenzaldoxime* (7g), a white solid, m.p. 46—48° (Found: C, 78.5; H, 5.6; N, 7.2. $C_{13}H_{11}NO$ requires C, 79.2; H, 5.6; N, 7.1%), δ (CCl_4) 7.2—7.8 (m, 10 H) and 8.39 (s, 1 H); E-O-p-*nitrophenyl*-o-*nitrobenzaldoxime* (7h), a white *solid*, m.p. 147—148° (Found: C, 54.4; H, 3.3; N, 14.3. $C_{13}H_9N_3O_5$ requires C, 54.4; H, 3.2; N, 14.6%), δ (DMSO) 7.5—8.5 (q superimposed on m, 9 H) and 9.26 (s, 1 H).

E-O-*Methyl-ω-isonitrosoacetophenone* (7i).—A solution of sodium methoxide, prepared by dissolving sodium (1.15 g, 0.05 mol) in methanol (100 ml) was added to a solution of ω-isonitrosoacetophenone (7.45 g, 0.05 mol) in methanol (60 ml). The solvent was removed to leave the sodium salt of ω-isonitrosoacetophenone which was then covered with water (100 ml). Excess of dimethyl sulphate (14.5 g, 0.115 mol) was added and the solution was stirred for *ca.* 12 h at room temperature. An orange oil separated, which was extracted with ether. The ether was washed with 0.1N-HCl and then allowed to evaporate. The residue, a red oil, was steam distilled. The distillate was extracted with ether which was then dried ($MgSO_4$) and evaporated to leave a yellow oil (3.1 g, 38%). The oil was purified by fractional distillation *in vacuo*. The fraction which boiled at 82—90° and 2.5—3.0 mmHg was collected (lit.,[46] 152—153° at 60 mmHg). T.l.c. (silica gel; chloroform) of the product showed an intense spot, R_F 0.7, and a number of spots with lower R_F values. A sample of the compound with R_F 0.7 was separated using preparative t.l.c. This proved to be E-O-*methyl-ω-isonitrosoacetophenone* (7i) (Found: C, 66.1; H, 5.6; N, 8.1. $C_9H_9NO_2$ requires C, 66.3; H, 5.5; N, 8.6%), δ (CCl_4) 4.04 (s, 3 H), 7.4—7.65 (m, 3 H), 7.86 (s, 1 H), and 8.07—8.25 (m, 2 H). The n.m.r. spectrum of ω-isonitrosoacetophenone in [$^2H_6$]DMSO showed a multiplet at δ 7.5—8.05 and a singlet at 8.10.

Phenylglyoxynitrile.—ω-Isonitrisoacetophenone (4.47 g, 0.03 mol) was heated on a steam-bath with acetic anhydride (30 ml) for *ca.* 4 h. The solution was then fractionally distilled *in vacuo*. The acetic anhydride distilled between 36—44° at 15 mmHg. The temperature then rose rapidly and the nitrile distilled in the range 62—68° at 4 mmHg (lit.,[75] 206—208, 207—210° at 760 mmHg) (Found: C, 72.7; H, 4.0; N, 10.3. C_8H_5NO requires C, 73.2; H, 3.8; N, 10.7%). $\bar{\nu}_{max.}$ (thin film) 2 220 cm^{-1} (C≡N), δ (CCl_4) 7.5—8.0 (m, 3 H) and 8.1—8.3 (m, 3 H).

Kinetic Method.—The rates of elimination of the ethers (7) and (8) were followed by 4 : 1 water–dioxan at 25° by following an increase/decrease in absorption at suitable wavelengths. The wavelength was selected following preliminary repetitive scans of the u.v. region. Tight isosbestic points were observed in all cases (with the exception noted in the text). The wavelengths used to follow the course of the reactions are noted in Table 1. Kinetic runs were initiated by adding 1 or 2 drops of the substrate which was made up (10^{-2}M) in dioxan to a pre-equilibrated solution buffered at the required pH. A Perkin-Elmer model 124 or Unicam SP 800 B spectrophotometer (both fitted with thermostattable cell holders and external recorders) was used to follow optical density changes. The rate constants quoted in Table 1 were obtained for the optical density–time plots by a graphical method and are average values (±5%) obtained from several (minimum three) determinations. Other details are as previously described.[76]

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